FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF

THE DENTAL PLAQUE SUBCOMMITTEE OF

THE NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

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C O N T E N T S

P R O C E E D I N G S

(8:37 a.m.)

DR. GENCO: Good morning. I'd like to call this meeting to order.

First on the agenda is a conflict of interest statement by Dr. Neal.

DR. NEAL: The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of a conflict.

During the next several years, the subcommittee will review information on ingredients contained in products bearing antiplaque and antiplaque-related claims to determine whether these products are safe and effective and not misbranded for their labeled use.

Since the issues to be discussed by the subcommittee will not have a unique impact on any particular firm or product, but rather may have widespread implications with respect to an entire class of products, in accordance with 18 U.S. Code 208(b), waivers have been granted to each member and consultant participating in the subcommittee meeting. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

Thank you.

DR. GENCO: Thank you.

It appears that we are -- Bob?

MR. SHERMAN: Excuse me, Bob. I just wanted to, for the record, repeat an announcement that I made yesterday morning regarding the review of foreign marketing data, and that is, if there's any objection to the public review of data before the eligibility of those data where the monograph system is determined, sponsors may withdraw those data from the review.

They would then be required to repetition the agency and show just cause for reopening the administrative record and reaccepting the data.

DR. GENCO: Thank you.

It appears that we're coming to the point now,

having voted on pretty much all of the agents, with the exception of one or two, that we had been assigned, and having some in Category I that we will be discussing labeling -- we talked about that yesterday -- and final formulation, and that is going to be the topic of this morning.

We'd like to have Dr. Scott McClanahan come to the podium to make a presentation on final formula testing from Colgate.

No? I thought that Scott works for another company. Okay, good.

(Laughter.)

DR. McCAIN: It's okay, Bob. Just a minor oversight.

(Laughter.)

DR. McCAIN: Thank you, Bob and members of the committee. Good morning. My name is Hulon McCain and I work for Colgate-Palmolive Company, not Procter.

We appreciate this opportunity this morning to offer just a few very brief comments on final formulation testing as you, the subcommittee, deliberate this issue this morning.

As Dr. Bowen indicated yesterday, as you touched on this issue before, this will be a huge problem before the committee which you'll have to face for this

category. The final monograph will list accepted Category I ingredients and concentrations or ranges of concentrations which have been determined to be safe and effective for the control of gingivitis, and gingivitis is the accepted clinical endpoint for this category.

Then the question to consider today is this. Should manufacturers test their final formulated products to assure themselves and the American consumer that the marketed products are effective and safe as claimed?

Colgate believes the answer to this for this monograph is yes and that in the preceding review of the submitted data, this conclusion has already been reached by this subcommittee for specific ingredients.

For example, for cetylpyridinium chloride, CPC, one of the three Category I ingredients so far in this category, there was considerable discussion by the subcommittee in several presentations regarding clinical effectiveness of formulations used by two different manufacturers.

The thread, the theme running throughout this discussion was that there were minor differences in the formulations that were submitted by the two manufacturers and these minor differences produced in one case a clinically efficacious product and in the other an ineffective product.

Certainly at least in this instance -- and Colgate believes in most instances -- with this category clinical effectiveness of CPC products is formulation-specific and testing is required to ensure that only effective products are marketed to the consumer.

The fundamental issue then for Colgate is not whether final formulation testing should be mandated but it is what kind of testing should be mandated for this category to assure antigingivitis activity of the final products. And antigingivitis activity is the only clinically significant endpoint for this category. This has been reviewed several times by this subcommittee.

Furthermore, the only validated, widely accepted technique for reliably demonstrating antigingivitis activity of final formulations is a 6-month clinical trial. This type testing with inclusion of a microbiologic component to assure safety reliably confirms expected actions of the final product when this product is used by an OTC population throughout their lifetime.

There are no accepted surrogate endpoints at this time for gingivitis, not plaque, not antibacterial activity, or any of the other numerous pharmacologic activities of the ingredients reviewed to date. However, there are numerous predictive models in use and which are helpful in developing ingredient and formulation candidates

for confirmatory clinical testing. These predictive models include, but are certainly not limited to, disk retention assays, plaque glycolysis assays, plaque regrowth assays, and numerous short-term plaque and gingivitis clinical studies. These tests in our opinion should not be used as a substitute for adequate clinical testing that's required to demonstrate safety and efficacy of the marketed products which will be used by the consumer throughout their lifetime.

Colgate respectfully submits the following recommendations regarding formulation testing for your consideration today.

Number one, gingivitis is the only clinically significant endpoint for activity of Category I ingredients.

Number two, there are no surrogate endpoints, validated or widely accepted, that are available for gingivitis, to demonstrate gingivitis.

Number three, the only validated, generally accepted method for reliably demonstrating expected consumer benefits from antigingivitis products is the 6-month clinical trial.

And lastly, regarding the secondary antiplaque claim, which has been discussed, the subcommittee has determined that all allowed antiplaque claims are

therapeutic claims. Therefore, the clinical demonstration of these effects should rightfully be made only in association with the antigingivitis effects; that is, they should be demonstrated in the same clinical trial.

I'd like to close today with a summary quote from a 1997 publication evaluating two of the predictive models which have been posed to the subcommittee for final formulation testing, and the quote is this. Although these methods, the predictive methods, can enhance probability of achieving clinical success, it is always necessary to conduct well-controlled clinical trials to fully assess the efficacy of mouthwash products. This is a position that Colgate fully agrees with and urges the subcommittee to consider adopting a similar one.

Thank you, Mr. Chairman and committee.

DR. GENCO: Thank you, Dr. McCain.

Comments, questions from the panel?

(No response.)

DR. GENCO: It's a very clear stand. Does anybody want to discuss that? Bill?

DR. BOWEN: Would you agree that the incompatibility of CPC with the formulation that was submitted could have been foreseen and that any other bio-incompatibilities would be well recognized given the well-known structure and the properties of CPC? I'm using CPC

obviously as an example.

DR. McCAIN: Right. I do agree that in retrospect, after we've seen the data, we might have been able to predict that, but just as we probably were not able to predict that in advance, I would submit to you that we may also not be able to predict other incompatibilities. These data were reviewed only for two or three formulations. When this product is marketed by other manufacturers, there are a myriad of different ingredients that may be included and incompatibilities which may occur.

DR. GENCO: Would you agree that the incompatibilities could be detected by, say, a biochemical method such as HPLC or NMR and that a simple test in the mouth of rinsing with the formulated product and determine the bioavailability of the active ingredient? Would that not suffice?

DR. McCAIN: I would submit, Bill, that the only way to determine final effectiveness for the consumer of these products is to do clinical testing for those products. Gingivitis is the clinical endpoint for the category. There are no surrogates. Free versus bound CPC, for example, is not a surrogate. Antibacterial activity is not a surrogate. Antiplaque activities are not surrogates. So, Colgate's position is that clinical testing is necessary to demonstrate antigingivitis effects for these

products.

DR. GENCO: Go ahead.

DR. OKARMA: Thank you, Mr. Chairman. If I might just add a few more comments to what Hulon has already said.

The CPC example is merely just one example. We've seen this throughout several of the products that have been reviewed. For example, SLS, sodium lauryl sulfate, was reviewed, a well-known ingredient used in formulated products on the OTC market. The product has a demonstrable plaque effect. The product does not have a gingivitis effect. Therefore, we would caution against the use of plaque in and of itself as a surrogate for the clinically significant endpoint of gingivitis.

We as a company are the holder of the first approved abbreviated new drug application for a chlorhexidine rinse. The difficulties of formulating with chlorhexidine are certainly well known. We entered into, believe me, lengthy discussions with the Food and Drug Administration during the approval process for that ANDA, and the issue was one of how do we demonstrate that our product is bioequivalent to the innovator product. The net result of these discussions was that there is no validated surrogate for the clinically significant endpoint of gingivitis, such that the only thing that can be done is a

bioequivalence study with a clinical endpoint, namely gingivitis.

Thank you.

DR. GENCO: Would you please state your name for the record?

DR. OKARMA: Yes. I'm sorry. Paul Okarma, Colgate-Palmolive Company.

DR. GENCO: Thank you, Paul.

Bill, further comments? Any further comments or questions from the panel?

DR. DOYLE: Yes. I'm Dr. Matt Doyle. I'm Associate Director and Senior Researcher for Procter & Gamble research and product development worldwide.

I appreciate Colgate quoting our work.

(Laughter.)

DR. DOYLE: We need to place that in the proper context. The paper which they were quoting was a descriptive method on the DRA, particularly as presented before this committee relating to the CPC application.

What I do want to point out is that the assay itself was meant to assess and does assess chemical availability of CPC. You'll recall that I counseled this group that a series of testing that was required to establish the suitability of products and active ingredients included biological effectiveness tests which,

when coupled with chemical availability assessments, do adequately predict clinical performance of CPC-containing products.

DR. GENCO: Could you expand on what you would recommend for biologic effectiveness testing?

DR. DOYLE: Well, I think the panel has before it a document which we have prepared and it's fairly thoroughly outlined there.

DR. GENCO: Just animal testing, short-term human clinical trial? What do you mean?

DR. DOYLE: We believe that it has to be an ingredient-specific assessment made on the types of testing, that the diverse mechanisms of action that we're looking at, be they anti-inflammatory, antimicrobial, astringents, anti-adherence -- you guys went through that yesterday yourselves quite eloquently. There will be no single test that covers that broad spectrum. So, you're really going to need to take, in my opinion, our opinion, an ingredient-by-ingredient or class-by-class approach to this. In fact, there are rational and reasonable approaches to it, and that's our position.

DR. GENCO: Short of full 6-month clinical trials.

DR. DOYLE: Short of full 6-month clinical testing.

DR. GENCO: So, that's your stand.

DR. DOYLE: That's correct.

DR. GENCO: Bill?

DR. BOWEN: Could I ask you an additional question? Supposing somebody adds fluoride to an approved formulation of CPC, what's your attitude towards testing of that product?

DR. McCAIN: For combination products, generally subcommittees have required data to support those combinations. We also would suggest data to support those, demonstrating whatever is required under the anticaries monograph, number one, and also whatever the subcommittee decides regarding the need for clinical testing for the antiplaque/antigingivitis activities. Colgate believes that that would be clinical trials.

DR. BOWEN: So, if I understand you correctly, you would want a full 2-year clinical study of the effectiveness of fluoride in that mixture.

DR. McCAIN: No. The anticaries monograph does not require that to demonstrate anticaries. The anticaries monograph at this point only requires animal caries testing uptake soluble to reduction testing. But certainly for the antiplaque category, to demonstrate antigingivitis effects we would recommend a clinical test to do that.

DR. BOWEN: But does the anticaries monograph

-- I read it but I don't remember -- deal with a combination of products?

DR. McCAIN: There is a combination policy in place. At this point it only deals, to my knowledge, with hypersensitivity products and fluoride.

DR. BOWEN: Thank you.

DR. GENCO: Comments, further comments, questions from the panel?

(No response.)

DR. GENCO: If not, thank you very much.

DR. McCAIN: Thank you.

DR. GENCO: Two other individuals have asked to speak from industry. David Morrison from Chesebrough-Ponds, do you still want to speak, or have the issues that you wanted to discuss been brought up?

MR. MORRISON: Thank you. I'm David Morrison from Unilever United States representing Chesebrough-Ponds. I've submitted a document describing our position with respect to final formulation testing. I'd just like to place what this panel is reviewing right now in a little perspective.

Under the monograph process, the agency has reviewed 43 categories and subcategories of OTC drugs, and there have only been 7 categories of drug where the FDA has or the panels have recommended or the FDA are requiring any

form of final formulation testing. That final formulation testing is only required where the active ingredient is effective by minor variations in final formulation testing.

So, for example, the final final testing is not required in any of the following OTC drugs: topical antimicrobial, antibiotic, antifungal, anti-acne, or diaper rash products, laxatives, antidiarrheal products, antiemetics, sleep aids, stimulants, cough/colds, optics, anal/rectals, skin protectant, external analgesic, oral health care antiseptics, astringents, debriding agents, demulsants, tooth desensitizers, and many others. This is really consistent with the original intent of the OTC monograph process.

So, we would urge you, when you're evaluating the establishment of final formulation testing, to require this final formulation testing only where the evidence the panel has reviewed demonstrates on an ingredient-by-ingredient basis that this extraordinary testing requirement is required.

If you do determine that final formulation testing is required for these antigingivitis products, we think that you need to make it active ingredient-specific because not all the ingredients are completed. We as Unilever are supporting some of the other technologies, the baking soda, peroxide, zinc citrate, and we're still

conducting those studies which will be submitted to you at an appropriate time. The testing that might be required for a CPC product might not be appropriate for a zinc citrate product.

So, we believe it's premature and inappropriate to conclude that the effectiveness of all antigingivitis active ingredients will be negatively affected by minor variations in formulation.

If you determine that it is necessary to take this unusual step, you might look at other monographs to see how they've dealt with final formulation testing, and these testing requirements in these seven other instances vary. They're specifically tailored to the active ingredient.

For example, the external analgesics require only dissolution testing as a final formulation test. Other tests might be bioavailability tests, much as the anticaries fluoride uptake test would be. So, really the establishment of final formulation testing, which is active ingredient-specific, isn't really groundbreaking. Internal analgesics can have acquired final formulation testing only for certain active ingredients in the monograph or certain combinations, and topical antimicrobials totally exempt certain active ingredients from any final formulation testing.

The next thing that we think you need to consider is that these final formulation tests should be cost effective, scientifically sound, and we believe that they can be in vivo, in vitro, and ex vivo validated surrogates for the stability and bioavailability of the active ingredient within the final formulation.

So, for Category I status, this panel has determined that 6-month clinical trials are the standard that you have to meet in order to demonstrate that the active ingredient is effective, but we don't believe that should be the appropriate final formulation testing. We believe that you've already determined that the active ingredient is effective, and now what you have to determine is that nothing has complexed with that active ingredient which decreases its activity.

In fact, the FDA has addressed whether lengthy and costly clinical trials should be used as final formulation tests, and in fact in the preamble to the anticaries monograph -- I'll quote it here. It is not in the best interest of consumers or industry to require additional clinical testing of Category I active ingredients because of formulation changes that can be demonstrated in the laboratory to be inconsequential and not to interfere with the effectiveness of dentifrices. The agency agrees with the comments and the panel that the

requirement of lengthy trials is no longer warranted and that appropriate laboratory testing is adequate to assure the effectiveness of fluoride dentifrice containing Category I active ingredients.

The suggestion that final formulation testing should take the form of two 6-month gingivitis trials with a full microbial component places a costing of that final formulation testing around $3 million, and we just don't believe that that type of final formulation testing for minor changes in a formula is appropriate.

So, I guess we would urge the panel, as it reviews this establishment of final formulation testing, to first make it active ingredient-specific and, second, to follow this precedent and apply this only where the evidence the panel has reviewed mandates this truly exceptional final formulation testing requirement.

Thank you.

DR. GENCO: Thank you, Dr. Morrison.

Comments, questions from the panel? Bill?

DR. BOWEN: How would you define minor changes in formulation?

MR. MORRISON: What I would consider a minor change in the formulation might be the addition of another cosmetic ingredient, a breath-freshening ingredient, something that isn't a change in the abrasive system. It's

not a change in the active ingredient. It's a minor change.

DR. GENCO: Just for the record, the caries requirement is caries reduction and one of the following tests: reduction of enamel solubility or fluoride enamel uptake.

Also, as I understand, the caries clinical trials are somewhat on the order of several years, two years. So, just to put that into perspective.

What we're talking about, one alternative, is a 6-month clinical trial versus a 2-year trial for caries, so that the cost would obviously be quite different.

MR. MORRISON: Correct.

DR. GENCO: Thank you.

Comments, questions? Lew?

MR. CANCRO: Just a comment, Bob, that the terminology, a 6-month trial, only refers to the period in which the active is with the group, and that's the period it's tested for. But a clinical trial of 6 months will take a run-in period, organization, so that in time it's never 6 months.

DR. GENCO: I just wanted to make the difference. The same thing would happen with a caries trial. So, it never takes 2 years. It takes more than 2 years. I'm not taking a stand here. I just want to make

that clear. One of the justifications for doing something other than the clinical trial for caries was the cost of the caries trial. I'm saying that might possibly be more expensive, considerably more, than the gingivitis trial.

MR. CANCRO: Yes. I'm only commenting on the use of the term "6 months." We all quote that and there's a thought that 6 months later you have the answer. Well, if you work with business units, you never give them an answer in 6 months. It's more like a year.

DR. GENCO: Thank you.

MR. MORRISON: Dr. Genco?

DR. GENCO: Yes.

MR. MORRISON: If your question was the difference between the full caries trial, which would be a several-year trial and several-million-dollar test, and if the complement of testing that's required under the anticaries monograph, the order of magnitude is significantly less. It costs I believe on the order of $100,000 to do the complete testing for anticaries that's required now, and a 3 to 4-year anticaries clinical trial would be in the millions.

DR. GENCO: Thank you.

Dr. Curro?

DR. CURRO: Yes. I just have a general comment on the demands that we place on these compounds from a

pharmacological viewpoint. I'm not aware of any area in pharmacology where we have these demands. We usually have an active drug. It's a targeted endpoint.

But when you think about a dentifrice or a mouthwash and you think about the multiplicity of actives that are in there and when you think about that it's applied by a vehicle in an environment where it's being constantly diluted and then expectorated and no one knows what the lag time is, it defies essentially the pharmacokinetics of how we view drug action.

The complexity of trying to establish all of these endpoints in one clinical study becomes almost impossible. If you design a clinical study with more than three or four cells, it becomes exceedingly burdensome. Never mind what the cost is. It's just a matter of the operational style of it.

But the actual activities of all these agents that we place, abrasives and fluorides and whitening agents and antigingivitis agents and fluoride, et cetera, nowhere in pharmacology do you have that kind of myriad of active ingredients in one compound.

So, when you deliberate about establishing all of these endpoints, somewhere science has to step in and alleviate some of the burden, otherwise these products will not be developed or just fall out. So, I just add that as

a comment.

DR. GENCO: Are you advising that we look carefully at surrogates and not simply rely on the so-called 6-month clinical trial?

DR. CURRO: Yes.

DR. GENCO: Look carefully at scientific validity of possible surrogates.

DR. CURRO: Exactly.

DR. GENCO: Comments, questions?

(No response.)

DR. GENCO: Okay, thank you, Dr. Morrison.

Greg Collier, do you want to make a presentation? Dr. Collier is with Procter & Gamble. I'll get it straight. I got my name straight, my children. I'm working on my grandchildren. I apologize.

(Laughter.)

DR. COLLIER: My name is Greg Collier. I'm Section Head, Regulatory Affairs with Procter & Gamble Company.

I guess you guys are going to get all sides of this. I went to my first hockey game last evening. So, I guess in hockey terminology, you're getting a hat trick on formulation testing.

(Laughter.)

DR. COLLIER: I'd like to briefly summarize the

position that we've submitted in writing to the panel and build on some of the points that Dr. Doyle made. We've addressed this in depth in our previous ingredient submissions, especially for CPC where this was a major topic of discussion. So, Procter & Gamble's position on this has not changed at all. I think we're being very consistent.

I'd like to make four key points to begin with.

First, we certainly agree that all ingredients must be established as safe and effective by rigorous clinical testing. I don't think there's any argument about that.

Performance tests should not be regarded as surrogates for this rigorous testing, nor should they be regarded as surrogates for evaluating differences in active ingredients. This is the role of clinical testing.

However, once the safety and effectiveness, though, has been established by clinical testing and reviewed by the panel and the ingredient deemed safe and effective, we certainly believe that combination in vitro/in vivo performance testing standards can be developed and validated to adequately ensure the ingredient availability and effectiveness in final product formulations.

Further, we do not think at this point that

full clinical testing is required to validate most formulation changes in final finished products.

And as consistent with several other monographs, we think that the establishment of performance testing is a critical aspect to this plaque and gingivitis monograph because it will ensure that future formula variations will not deleteriously influence the established effectiveness of the active ingredient.

There may not be a single-performance test and there probably won't be a single-performance test or test regimen to adequately address the variety of agents that you're looking at in this field. There are varying mechanisms of action, but we believe the performance testing should be addressed for each ingredient on an ingredient-specific basis and that testing should be conducted against the positive control, USP reference standard containing the same ingredient as the test product.

We recommend that ingredient sponsors should be responsible for proposing the relevant performance test for their ingredients, providing adequate validation information for these proposed tests, and defining appropriate USP reference standards for their test materials.

Our experience would suggest that performance

testing regimens for antimicrobial-based, antiplaque and antigingivitis formulations at a minimum should include, first, confirmation of the available antimicrobial in the formulation and, second, demonstration of chemical and/or biological effectiveness correlated with clinical efficacy.

This can be accomplished by a combination of one in vitro and at least one in vivo test or two in vivo tests, should the sponsors determine that appropriate. But these tests should demonstrate ability to differentiate activity between clinically proven active product formulations and placebo and, secondly, ability to demonstrate sensitivity to deactivation of the formulation.

We believe that we satisfied this criteria for stannous fluoride and CPC and have presented data to the panel and have presented the methods that we've used to the panel. These methods have been published in peer-reviewed journals also.

For stannous fluoride dentifrices, we recommend as adequate a combination of soluble stannous, soluble fluoride, and PGRM testing. That's the plaque, glycolysis and regrowth methodology.

The in vitro assessment of soluble stannous in combination with the in vivo treatment/ex vivo measurement of PGRM activity provide excellent correlation with clinical activity of stannous fluoride dentifrice

formulations.

For CPC mouthrinses, we recommend as adequate a combination of again PGRM, soluble, quaternary ammonium salt levels, and disk retention assay, or DRA, which again the combination provides excellent correlation with our clinical results.

As I stated, both the PGRM and DRA methodologies have been published.

In summary, our position is once the safety and effectiveness of an ingredient has been established via the monograph review process, we believe that a combination of in vitro and in vivo performance tests can be defined and adequately validated to ensure availability and effectiveness of an active ingredient in a finished product. We believe that performance testing standards are in keeping with the spirit of the monograph process and that full gingivitis testing is not required to validate most final formulation changes.

Finally, we have developed performance testing standards for both stannous fluoride and CPC. We've validated these tests against clinical results, and we currently utilize these performance tests to internally qualify our stannous fluoride and CPC formulations.

Thank you for your attention, and I'd be happy to address any questions.

DR. GENCO: Thank you, Dr. Collier.

Any comments, questions from the panel? Bill?

DR. BOWEN: Would you therefore be in favor of when a new agent is being submitted for Category I approval, that the submitter be required to submit performance testing standards at the same time?

DR. COLLIER: Yes, that would be our recommendation, maybe not at the same time, but during the process. We're saying that the sponsor should identify those tests. They understand their formulations better than anyone. They understand what makes them work, what deactivates them, and they're in the best position to recommend the testing.

DR. GENCO: Okay, if there are no further questions, we thank you very much.

Now I'd like to ask Debbie Lumpkins to make a presentation on this topic. She's from the Division of Over-the-Counter Drug Products of the FDA.

MS. LUMPKINS: Thank you, Mr. Chairman, and good morning.

I've been asked to give you some background information on final formulation testing in the OTC drug review. I will be briefly discussing USP final formulation testing, final formulation testing under the OTC drug review, the recommendations of the Advisory Review Panel on

OTC Oral Cavity Drug Products, or the Oral Cavity Panel, and anticaries final formulation testing requirements.

Once an active ingredient is included in the OTC final monograph for a particular use, no further proof the ingredient's effectiveness for that use is required to be submitted to the agency.

However, the agency now requires that OTC drug active ingredients have the United States Pharmacopeia, or USP, standard as a condition for inclusion in an OTC final monograph. These USP standards define the quality and purity of the active ingredients, as well as any testing needed to determine compliance with the standard.

There are also USP monographs for dosage forms of some of the active ingredients and combinations in the review that also require final formulation testing. In general, USP standards for final formulation testing for OTC drug products subject to the review are limited to systemic products.

In some cases, compliance with the USP final formulation testing requirements for particular dosage forms have been included in an OTC monograph. One example of this is the agency's proposed requirement that aspirin tablets comply with USP dissolution standards for this dosage form.

Over the course of the OTC drug review, the

agency has received recommendations for a number of panels concerning the need for effectiveness testing of final formulated products. The final formulation testing has been proposed or required for the following drug product categories.

I'll not give you the details of all the final formulation testing requirements in the review. Instead, I will try to give you an overview of final formulation testing.

In general, final formulation testing has been required for OTC drug product categories where a formulation has been shown to have a substantial impact on the effectiveness of the active ingredient. Final formulation testing is intended as an alternative to clinical trials to address such effectiveness issues.

As this slide shows, final formulation testing in the review has taken a variety of forms. It can range from simple in vitro tests to the combination of in vitro and in vivo and can even involve human studies.

DR. LISTGARTEN: Before you leave this what's the difference between health care antiseptics and oral health care antimicrobials?

MS. LUMPKINS: The oral health care ingredients are products intended to reduce the risk of infection of minor wounds in the oral cavity. The health care

antiseptics are largely, not all, but largely professional use products intended for use prior to surgery or in between patient examinations, that kind of a thing.

DR. GENCO: Excuse me. I'd ask you to use the mike. I know it's difficult to remember.

That was Dr. Listgarten. He asked the question what's the difference between oral health care antimicrobials and health care antiseptics.

MS. LUMPKINS: The next slide shows the drug product categories that include human testing. Final formulation testing also includes effectiveness standards, and products marketed under the monograph are expected to be able to meet these standards. However, manufacturers are not required to submit the results of testing, but should have the data from such tests on file.

Now that I've given you the overview, I would like to get more specific and discuss the recommendations of the Oral Cavity Panel.

DR. GENCO: Deborah, could you go back? The human testing. Could you just go back and let's take a look at that one again? Thank you so much.

So, these are human studies only or is there some in vivo/in vitro also?

MS. LUMPKINS: There's a mixture. The antiperspirant is a gravimetric test. It's a hot room

test. You measure the reduction in perspiration.

The health care antiseptic is a combination of both in vitro and in vivo testing. It's not quite a full-blown clinical trial. It's handwashing tests, cup scrubbing methodologies, that kind of a thing.

The sunscreen is only in humans and basically it's a reduction of the light transmission through the sunscreen.

DR. GENCO: Are there any human studies that are as intensive as the original study proving efficacy?

MS. LUMPKINS: No.

DR. GENCO: Thank you.

MS. LUMPKINS: The charge to the Oral Cavity Panel was the review of active ingredients for the treatment of sore mouth and sore throat. The panel did not specifically evaluate the effectiveness of antimicrobial ingredients to inhibit plaque formation. However, during the course of its deliberations, the panel was presented with effectiveness testing of antimicrobial mouthwash formulations. These effectiveness tests included a plaque reduction criterion as a measure of antimicrobial activity.

The majority of the panel concluded that given the scope of the panel's charge, plaque reduction would not be an appropriate measure of the antimicrobial activity of the mouthwash formulations. The minority of the panel,

however, was concerned that no advisory committee had jurisdiction over antiplaque claims and that manufacturers would have no direction or guidelines to prove the effectiveness of mouthwash formulations for killing bacteria in the oral cavity.

The Oral Cavity Panel report included minority recommendations on testing. These recommendations included both in vitro and vivo testing. The in vivo testing consisted of a modified chlorhexidine gluconate coefficient test against Streptococcus mutans, Actinomyces viscosus, Candida albicans, and Pseudomonas aeruginosa, if necessary.

The panel minority's recommendation for in vivo testing was the direct sampling of dental plaque from designated areas of the tooth and gingival surface.

In its evaluation of the panel's recommendations, the agency decided not to adopt the minority recommendations. However, in 1994 the agency published its proposed rule for OTC antimicrobial oral health care products. In that proposed rule, the agency included testing for OTC antimicrobial oral health care products indicated to reduce the risk of infection in oral wounds.

The highlights of this proposed testing are that it is an in vitro test and it has an effectiveness criteria of a 3 log 10 reduction within 10 minutes at 37

degrees Centigrade in the presence of 10 percent serum.

This brings me to the subject of the testing required for the OTC anticaries drug products. Anticaries drug products containing fluoride are currently required to demonstrate their effectiveness through both in vivo and in vitro testing as follows. There is a laboratory testing profile to demonstrate an adequate level of fluoride ion, and there are biological animal tests of enamel solubility reduction and fluoride enamel uptake.

As you can see, there are a variety of final formulation testing under the review. However, the underlying principle behind all of it is the need to verify the activity of the active ingredient when formulation effects are of concern.

That's about all. Does anyone have any questions?

DR. GENCO: Lew?

MR. CANCRO: I just wanted to make sure that Debbie's presentation is available, the slides and the presentation.

DR. GENCO: Any comments, questions from the panel? Max?

DR. LISTGARTEN: I think there may be a difference between evaluating effect on bacteria when you're concerned about oral cavity wounds and when you're

concerned about dental plaque. In one case, you have a biofilm. In the other case, you may have more of a planktonic suspension of bacteria, and there may be several order of magnitude difference in trying to kill bacteria in one versus the other. So, if you're going to look at plaque, you may have to adopt different standards.

MS. LUMPKINS: The in vitro test for the oral health care I put in there more or less to show you the scope of what final formulation testing can take. I wanted to make sure that you were aware of all of the various ways in which these products can be tested from something as simple as a single in vitro test all the way through the human. There's a big spectrum there.

DR. GENCO: It has been very helpful and you've done that very nicely, Debbie.

Just so we understand the anticaries testing, fluoride like any other drug in an OTC product would have to be demonstrated to be there. So, it's like the aspirin and acetylsalicylic acid, et cetera. So, that's what that first one is. In this toothpaste or what have you, there has to be adequate fluoride ion by chemical testing.

MS. LUMPKINS: Right.

DR. GENCO: And then there's an alternate, either enamel solubility reduction or fluoride enamel. These are in vivo human --

MS. LUMPKINS: Right. They're animal --

DR. GENCO: Oh, they're animal testing. Okay.

MS. LUMPKINS: In rats.

DR. GENCO: So, in rats enamel solubility reduction and fluoride enamel uptake.

And then the animal anticaries is a rat experiment too. Is that true?

MS. LUMPKINS: Yes. You have to be able to demonstrate, using one of these two biological methods, a reduction in caries.

DR. GENCO: Okay, thank you.

Further comments from the panel or questions of Debbie? Yes.

DR. WHITE: Hi, Bob. Don White, Procter & Gamble. I'm Principal Research Scientist.

I think in the caries monograph, I think the animal caries test is the in vivo test. The enamel solubility reduction and fluoride uptake would typically either be -- the ESR is an in vitro test, to be sure. You treat enamel and you measure solubility. The fluoride enamel uptake can be either an in vitro test or a denture chip type study.

Bill, is that your --

DR. BOWEN: That's correct.

DR. GENCO: Okay. So, the enamel solubility is

strictly in vitro.

MS. LUMPKINS: It can be.

DR. GENCO: You take a human enamel disk?

DR. WHITE: Well, I don't know.

MS. LUMPKINS: They're animal.

DR. WHITE: (Inaudible) in vivo (inaudible) are.

MS. LUMPKINS: The reg states that they're biological tests. Beyond that, I don't know.

DR. GENCO: Thank you.

Comments, questions?

(No response.)

DR. GENCO: I think we have a very thorough analysis of what has been done, and that's a very important perspective. Thank you very much.

DR. HYMAN: Bob?

DR. GENCO: Yes.

DR. HYMAN: We have seen submissions of enamel chips in an intraoral appliance in humans, so that might be an example of a hybrid.

DR. GENCO: Okay, thank you.

Now, is there any comments or discussion of what we've heard? Eventually we're going to have to make some sort of recommendation to the FDA with respect to final formulation testing.

What we might do -- we've heard a lot and there's a lot to think about -- we might discuss some general principles and then possibly between this meeting and next meeting break into a subgroup that could deal with the specifics. That's a suggestion. I'd like to bounce that off of you as a suggestion, but right now I think we have the time to discuss some general principles.

Well, to get the discussion going, we've had two extreme positions. One is full clinical trial for antigingivitis, reproducing the trial needed to prove efficacy. What is your feeling about that extreme? The other extreme would be some modification of a surrogate. The least would be maybe some in vitro testing. Then a combination of in vitro and in vivo.

Gene, do you want to start the discussion?

DR. SAVITT: Well, I'm concerned about the fact that we have products that may very well have mechanisms that vary quite a bit across a spectrum. At least in anticaries, you're dealing with one specific drug delivered, and therefore you can test for that specific drug. Here you're dealing with not only different drugs but drugs which have rather varying types of activity and mechanisms, and we have drugs that have gingivitis effects but not antiplaque effects. We have drugs that have both antiplaque and antigingivitis effects. While we currently

have a rather limited number that are in Category I in terms of effectiveness, there is a long list that are in Category III for effectiveness which are obviously being tested out there and may very well be added in the future to the Category I list which will in all possibility dramatically increase the variations in terms of mechanisms. I have a lot of reservations about making some sort of simplistic in vitro test to try to cover such variations.

DR. GENCO: All right. So, you make the point that it should be product-specific, whatever the final formulation testing.

And then you bring up the point of dealing with Category I and Category III.

What should we deal with? Let's say we end up with three Category I antigingivitis agents. Should we deal with those, possibly each having a specific final formulation procedural testing, or should we be more generic? Should we deal with all Category III and Category I? What is our challenge?

MS. LUMPKINS: The way that the agency has done it has usually been by drug product category. So, we've addressed antimicrobials -- and you may want to approach it that way, and wherever the product falls, it would have to test that way. By category as opposed to active

ingredients.

DR. GENCO: Antigingivitis is a general clinical active product group. In there, theoretically, there could be antimicrobial and that's how it becomes antigingivitis or anti-inflammatory. So, deal with those, the antimicrobial/antigingivitis, and the anti-inflammatory/antigingivitis, if it turns out that way, separately. Or alternatively, product by product, stannous fluoride versus CPC versus Listerine.

MS. LUMPKINS: Well, I think that if your concern is fluoride, you already have fluoride tests in place.

DR. GENCO: Let's first discuss the antigingivitis, and then as a separate discussion, the combination of antigingivitis with anti-fluoride with anti-sensitivity and other combinations, antitartar, so that we can keep it simple.

First, the antigingivitis, how to deal with that. Do we deal with each of the drugs in Category I? And it looks like there might be three different ones there. Talk about testing for each of those three.

MS. LUMPKINS: Right now you have an antimicrobial and you have fluoride in Category I and a combination. Right?

DR. GENCO: It's confusing because as I

understand, in the stannous fluoride antigingivitis effect is an antimicrobial effect. It happens to be a fluoride, but it's antimicrobial also.

MS. LUMPKINS: Absolutely.

DR. GENCO: And it is also anticaries.

If we just looked at it as an antigingivitis, it's an antimicrobial. It's thought to be an antimicrobial. So, you have two antimicrobials, CPC, stannous fluoride, and possibly a third, the combination of Listerine products which are probably antimicrobial. There's no indication that they're anti-inflammatory I don't think, and we should know that from the company from any other data if there is. So, really we have three antimicrobial/antigingivitis agents. Is that --

MR. CANCRO: Yes.

DR. GENCO: So, we could deal in your suggestion with the antimicrobial/antigingivitis agents as a group.

MS. LUMPKINS: As a group, yes.

DR. GENCO: For any antimicrobial/antigingivitis agent here are the performance standards. Okay, that's an approach. Does that have appeal?

That means we're only looking at Category I. And Category III, if we should look at Category III --

MS. LUMPKINS: Well, I think if you can make allowances to upgrade other -- in other words, if you can identify the classes --

DR. GENCO: In Category III.

MS. LUMPKINS: -- antimicrobial, abrasive, astringent, and decide for which type of activity you need to have some verification.

DR. GENCO: So, we look at Category III and there may be another one or two activities there.

MS. LUMPKINS: Right.

DR. GENCO: And that would be more theoretical though because those have not been shown to be effective. Okay.

Lew, does this seem to be a reasonable approach? We're not talking about the combination now.

MR. CANCRO: No, no.

DR. GENCO: Except for the culmination within the antigingivitis. Okay.

MR. CANCRO: Right. I think you've hit on what I feel is necessary and that's the broadest approach because this is a living process. This is a process where through the years supplemental data can come in and hence whatever you decide, whatever way you go, that would have to be in place for those materials to come in. You've set the standard as to what they must achieve, but again should

those III's become I's and now there's formulation changes, then whatever you set today, or whenever you're going to set that principle, must be broad enough to include those also I think.

MS. LUMPKINS: There's also something that I didn't mention in my presentation that I should have. If for some reason the tests that have been proposed don't work for the formulation -- we found that with some of the health care, some of the manufacturers have been saying, my product is not soluble in water or this is a problem for MIC determinations. We do allow manufacturers to develop their own methods of testing and submit them to us, and if we approve them, then they can test their products that way. So, there is some flexibility there.

DR. GENCO: So, we're to look at Category III, Category I, come up with best, state-of-the-art technology today based upon the science, but there is some flexibility for the future where they may be some unforseen activity or interference with activity of an addition. Okay.

It sounds like that's something we can't do around this table, though. I still think it needs some careful thought and investigation and maybe in between meetings have a subcommittee look at that. Does that seem a reasonable approach?

DR. KATZ: That would be reasonable. It's

whatever the panel itself is comfortable with at this point in time.

DR. GENCO: It would obviously be very open because that report would come back to this panel word for word.

Max?

DR. LISTGARTEN: I'm almost clear on single ingredients. If we have a single antiseptic all by itself, we can measure its activity in terms of antimicrobial effect using a variety of performance standards. Therefore, for single ingredients I don't have a problem with performance standards.

I seem to have a problem with the complex formulations that are eventually marketed in which we have a number of different agents doing different things. As was pointed out, if one has a brand new product, clinical trials are essential to demonstrate that the product works. This may include a dozen different ingredients in a particular formulation.

Now, if someone else wants to come along and change one of the ingredients, do they have to go through the same process all over again? I think that's the question. Is there flexibility or is there a mechanism where a manufacturer of a product can say my product is identical to product X which has been tested in clinical

trials, and all I'm doing is I'm changing the flavoring in this particular dentifrice. Do I really have to go through the entire business or is there a way where -- what do I have to do to convince you that adding a different flavor isn't going to make much difference?

This might be for one particular flavoring, and you can't put down regulations that will cover all possible variations because it could affect almost anything at different doses and so on. There should be some kind of a mechanism where one should be able to test on a case-by-case basis a situation and say, well, I think to satisfy us, this is what we need. But to set up regulations for every possible change seems to be an impossible task.

Can we devise some mechanism of a panel that will look at this and say, yes, I think you need to do this, that, and the other thing?

DR. GENCO: So, you're suggesting a case-by-case analysis. Now, isn't this what Debbie said, that there may be eventualities where we wouldn't cover the problem, that the FDA would look at it case by case?

I think if we use the anticaries as an example, fluoride, no matter what you add to that fluoride toothpaste, you can add whatever you want, it has to do three things. There has to be fluoride ion. It has to be either picked up by enamel or reduce enamel solubility, and

it has to reduce caries in rats. Period.

DR. LISTGARTEN: I'm happy with the fluoride story. I'm happy with fluorides and I'm happy in terms of caries.

DR. GENCO: You don't think we have a similar --

DR. LISTGARTEN: I think we're going to have a much harder time doing that for gingivitis.

DR. GENCO: Well, let's say CPC. No matter what you add to CPC, it has to do one, two, three, whatever we come up with.

DR. LISTGARTEN: What is it that we want from CPC?

DR. GENCO: Well, that's the challenge. The extremes are a full 6-month trial or some surrogate. That's our challenge. Or a set of surrogates or a combination.

DR. LISTGARTEN: Well, CPC is one of the -- we don't just have a fluoride ion with gingivitis products. We have CPCs, we have anti-inflammatory, we have antimicrobials that work in a whole variety of different ways. You can't pick on one mechanism and say as long as that ion is available and we can show that enamel doesn't dissolve as rapidly, then we're satisfied. I don't see anything like that --

DR. GENCO: What Debbie was saying is if we could look at categories of activity, antimicrobial -- now, there are three things that are antimicrobial, three products, CPC, stannous fluoride in its antimicrobial activity, and the fixed combination of Listerine, antimicrobial. So, now, anything antimicrobial that results in reduction of gingivitis would have to satisfy these performance criteria. This is what the suggestion is.

You're challenging whether we can do that even with the three that we've got on the table.

DR. LISTGARTEN: And there are others. There are many other antimicrobials that could conceivably come into the picture, and then there are anti-inflammatory agents.

DR. GENCO: Well, then that would be another group. We'd look at the Category III. Oh, there's a group of potential anti-inflammatories. Come up with another set of performance criteria conceivably.

DR. LISTGARTEN: Even if you look at the three we have, CPC, stannous fluoride -- what's the other one?

DR. GENCO: Listerine.

DR. LISTGARTEN: Listerine. If you look at these, they all have different mechanisms of action.

DR. GENCO: So, an alternate approach would be

-- and I think we got that advice this morning -- product-specific. Is that the term? Agent-specific. In other words, for agent X, here's the performance criteria, CPC. For agent Y, stannous fluoride, another set of performance criteria, maybe some overlap. That's another alternative.

DR. LISTGARTEN: We could do this but the minute you get into a situation where you have 12 ingredients and this is one of 12, and you're going to start to have interactions, I'm not sure how helpful this single ingredient evaluation or performance standard is going to be in judging a very complex mixture of various things.

DR. GENCO: You could take the extreme then and say it doesn't matter what you do, we want the 6-month clinical trial.

DR. LISTGARTEN: I don't want to take that extreme --

DR. GENCO: I know.

DR. LISTGARTEN: -- because it's not --

DR. GENCO: I understand that.

DR. LISTGARTEN: -- it's not in the best interest of the public or of anybody else.

DR. GENCO: So, the challenge is going to be to come up with something less than that.

DR. LISTGARTEN: But from a practical point of

view, the case-by-case review seems to make much more sense. It's going to address specific problems at a much lesser cost than trying to establish performance standards for all the possible permutations and combinations that you can come up with.

DR. GENCO: Of a so-called class even, even if we have classes, yes.

DR. LISTGARTEN: That's what I'm hung up with.

DR. GENCO: Yes. I think it's a good discussion. I think from what I've seen of the FDA performance criteria, their detail -- I mean, specifying media, time, et cetera.

MS. LUMPKINS: Some of them are.

DR. GENCO: So, there's nothing wrong with having a very detailed set of performance criteria probably in combination with advice from companies who have the actual laboratory experience in doing this. So, I don't see that as being a problem. We could be as detailed as we think is necessary, and the detail may be product by product by product.

DR. LISTGARTEN: I think depending on performance standards that different companies could submit, I think we could probably come up with a certain list that would help with guiding companies in developing products, but in the final analysis, I would like to see a

product-by-product evaluation.

DR. GENCO: Okay, Gene and then Bill and then Lew.

DR. SAVITT: I just wanted to point out that the essence to this problem is the essence that we struggled with for the first couple of years, which is that we don't know what the plaque reduction number is, this magical number. We don't know whether it's 15.8 percent or 22.6 percent, and if we knew that number, then they wouldn't have to go to the gingivitis testing. So, that same problem haunts us again.

But I would also agree with Max that it would be rather draconian to insist that if somebody wants to put spearmint instead of peppermint into a formulation, that they should have to go back and redo 6-month trials.

DR. GENCO: Bill?

DR. BOWEN: Yes. I agree with much of what has been said, and I think the problem is becoming I think a little clearer. I think most manufacturers when they're doing long-term clinical studies clearly monitor the changes that occur in the mouth as the test trial goes along. Again, I think we should require sooner or later that a testing profile be submitted at the time of application for approval based, presumably, on the postulated mechanism of action. Clearly, at this stage, we

can't foresee, for example, what's going to come down the road on totally different mechanisms of action, and obviously we can't anticipate the future.

One question I have for the periodontists on the panel is this. Is there a readily or widely accepted animal model for gingivitis?

DR. GENCO: I know that in many of the screenings, that the dog gingivitis assay is used, and that seems to be one that is reasonably reliably predictive of human activity.

Max?

DR. LISTGARTEN: It's probably cheaper to do it in humans and more reproducible.

(Laughter.)

DR. GENCO: And easier to get through the committees.

DR. LISTGARTEN: If you can do it in humans, don't do it in dogs.

DR. GENCO: In dogs, I think it's like a 1-month study or 2-month study.

DR. LISTGARTEN: It's the same in humans and cheaper.

DR. GENCO: Lew?

MR. CANCRO: Whatever test you come up with, be it the one end, the extreme, the clinical, or the other

extreme, there are a couple of essential points that are worth identifying. All of these drugs and all of the future drugs that get into Category I must demonstrate that they don't have a chemical interaction. That's part of the requirement. Even if they then subsequently go to clinical trial. No manufacturer will go to clinical trial with a known interaction.

Part of the requirement, probably in every category -- I guess Debbie can address this. I'm not familiar with all of them -- has got to be is the drug available at a concentration which you have declared is effective. That's the starting point. Thereafter, the testing, be it a clinical trial or whatever, but that's the starting point.

Another point of reference is that under the current system manufacturers do these tests. They're obliged to do them as the monograph is law, but they're not obliged to submit them to the FDA unless the FDA requests such a submission. So, be it a clinical trial or whatever it's going to be, the burden is on the manufacturer to have that evidence when he makes the change. There is no formal submission to the agency that we've done these tests, can we now market the product? That's not the way the system works.

DR. GENCO: I think, if I understand, Bill was

suggesting that that be done. It would have saved us all a lot of grief if that data had been available for CPC, but realize, some of those studies were done in the 1970s too and I think the experience of that has made us smarter, of course, in hindsight. But maybe we should make a recommendation based upon that experience with the submission, prior to approval, that that same kind of data be presented, which the companies have anyway. Is this what you're saying?

We're not talking about final formulation testing now.

MR. CANCRO: Yes. I'm not talking about the testing. I'm talking about an ingredient is Category I. Right? It's generally recognized as safe and effective. A manufacturer who didn't initially market that product wants to market it. Therefore, under the conditions you set, whatever they're going to be, concentration of the agent, whatever testing is necessary, he meets those conditions and markets his drug. There's not a formal clearance to use a generally recognized safe and effective ingredient. There's an obligation -- and you must comply with it -- to do the work.

DR. GENCO: Maybe I'm unclear on this. Let's say we heard a CPC-containing product of Procter & Gamble that was tested, has been put into Category I as safe and

effective based upon that particular formulation. Now, somebody else comes along -- I don't know if they can do this, but makes another CPC-containing product. Let's say another company. What's the process? Does that company have to come to the FDA with that product's testing and the final formulation testing that we're discussing?

MS. LUMPKINS: No. Once an ingredient is in Category I, the whole concept behind the monograph system is people don't have to come in. Manufacturer X provides the agency the data to put an ingredient in Category I. Once it's in a final monograph, any manufacturer out there can take that active ingredient and formulate it into a product without submitting any effectiveness or safety data for that product. They do have to comply with other regulations as far as good manufacturing practices and things like that and registration, but they don't have to submit any kind of data to us unless there's a problem.

DR. GENCO: Well, wait a minute. No. Don't they have to submit the data on the final formulation? For example, the anticaries. A new fluoride-containing toothpaste --

MS. LUMPKINS: They keep it on file.

DR. GENCO: Oh, I see, until challenged.

MS. LUMPKINS: That's right.

MR. SHERMAN: Yes. I was just going to say

they don't have to submit that data. They just have to have that data available.

DR. GENCO: So, what are you saying, Lew? They should submit it?

MR. CANCRO: No, no. I'm saying they're obliged to do the testing, whatever that testing is. Whatever conditions you set, they must do that to be in compliance with the monograph. That establishes that the ingredient in their product meets monograph conditions, and when it does, they market the product. But they do have to have that information in their own file.

DR. GENCO: So, that's what we're talking about. The final formulation performance standards would be those things that they have to do but they don't have to submit.

MR. CANCRO: They have to do. Right. There's no premarket clearance to putting a --

DR. GENCO: I thought you were suggesting they submit them.

MR. CANCRO: No, no.

DR. GENCO: Were you suggesting they submit them, Bill?

DR. BOWEN: Yes.

DR. GENCO: So, that's a change then in the whole OTC concept.

MS. LUMPKINS: Yes.

DR. GENCO: A good discussion.

Bill?

DR. BOWEN: In determining whether a new product is formed when you add two ingredients together, over what period of time? Is that specified?

MR. CANCRO: I'm sorry, Bill. I couldn't hear you.

DR. BOWEN: If you add, say, stannous fluoride and CPC in the same formulation, over what length of period do you have to study whether a new compound is formed?

MR. CANCRO: Well, to do that, it would have to meet the combinations that you set up. In other words, if somebody should decide to do that, you will have established that it is a rational combination, that they contribute something to the process, there's some benefit, there's not an increased risk, and additionally, for each of those ingredients, you will have set up a concentration, some sort of performance that they will have to meet. So, when a product comes out with two ingredients from the same pharmacological class, it has the burden of having already been recognized as being rational by this panel, as being appropriate.

Since nobody has submitted that, I don't know where you go from there, but that's a possibility.

Your question of an interaction, of course, is addressed by the immediate testing. Are they available in the formula? Do they meet the conditions that you've established they must meet? Then there's a shelf-life. There's usually a shelf-life period. That shelf-life, at least in the case of fluoride, has been based on stability studies at different temperatures in which you can demonstrate that the fluoride level in a dentifrice never falls below what is minimally effective. That is also established by the panel.

DR. BOWEN: Is there a shelf-life for any of the products that we've approved for Category I?

MR. CANCRO: You have to ask the manufacturers. I'm not aware.

DR. BOWEN: Does the FDA have any requirements?

MS. LUMPKINS: I think that the stability testing comes under the good manufacturing practice regulations.

DR. GENCO: So, we're not to be dealing with the good manufacturing practice regulations. So, we should get that clear.

MS. LUMPKINS: Yes.

DR. GENCO: The one thing that is within the realm of final formulation testing is presence of a presumably active component, in other words, like the

fluoride ion concentration such and such, but not its shelf-life. That's good manufacturing then.

MR. CANCRO: Yes. That's the first requirement. Then you go on to whatever testing you think is appropriate for the category.

DR. GENCO: Right, but we don't have to go into shelf-life and that sort of thing. That's good manufacturing or purity. We should get that clear.

MS. LUMPKINS: If you have concerns for particular ingredients, you are free to include whatever recommendations you think are appropriate, shelf-life, what have you. You can do that and it has been done in the past. It was done in the case of povidone/iodine in the health care antiseptic review.

DR. GENCO: If there's what? Something that would be particularly inhibitory to its activity, a --

MS. LUMPKINS: If you think it is a major problem that needs to go into the monograph, you can do that.

DR. GENCO: Well, I think we've got our tasks set out before us.

I'd like to suggest that we take a break and then come back in 15 minutes, finish this discussion, and we're going to check to see if the task group concept is a good one, and then maybe be thinking about if you want to

serve on this task group. Then we'll discuss the foreign ingredient assignments, and then we probably would be finished this morning I would guess.

DR. NEAL: I just want to clarify what you want to do with perhaps setting up some different task forces. Would you meet concurrently on different topics?

DR. GENCO: We've done this before actually. We haven't met. What we've done is talk by phone, exchanged documents, providing definitions, et cetera. Then one of the task group would come back to this group and present the full information about what was discussed. What I'm thinking of -- and we might take these in order. It seems logical that these performance criteria would be set, and then also another group working on labeling. I don't know if we assign two groups now or first the performance criteria, then maybe after next meeting, the labeling. So, either way. We can discuss that.

But you might be thinking about which one you'd want to participate in, or some of you might want to participate on both.

But I would think that might be an efficient way to handle these, which are really nitty-gritty wordsmithing and details of how these performance criteria are going to be carried out. A lot of that requires sitting at your desk looking at the literature, getting

input from industry. I would guess if Lew is on one or both of these task forces, he could be the conduit for information from industry, one possible conduit. Obviously, industry would have the ability to comment to the proposals made at the subsequent meetings. If that process is reasonable, I'd like you to think about it.

Somebody came up to the microphone. Yes, Rick?

DR. CURRO: You know, I think there's a precedent and the FDA may want to comment. There was a committee for in vitro release testing, which was chaired by Dr. Joel Zats, and companies that have creams and dermatological agents are in the process of developing this data. It seems that the procedure that you're faced with is very similar to what that program is about. So, you may want to go back and just look at that. They're in the process of generating data now.

DR. GENCO: Okay, fine. Thank you.

Obviously, this is not a simple issue as it was with fluoride. It's much more complex. We've only discussed the single ingredient or the combination within the class. We haven't discussed now if you add anticaries or if you add anti-hypersensitivity. I would challenge the task group to look at that too.

Yes.

MR. CANCRO: Bob, you say it's not as simple as

fluoride, but fluoride is only simple retrospectively. It was never simple at the time.

(Laughter.)

DR. GENCO: I'm sure. In retrospect it seems simple because there were some good minds behind it that came up with reasonable performance criteria.

Okay. Shall we take 15 minutes and get back here at 20 after 10:00? Thank you.

(Recess.)

DR. GENCO: I wonder if I might ask you to take your seats please.

Before we continue the discussion on final formulation testing, I'd like to again summarize the future activities as we have discussed.

It seems that the major issues that we yet have to deal with are final formulation testing, labeling, the consideration of the additional ingredients that have foreign data. That should certainly take us over the next year or so.

It seems that a logical order might be final formulation testing. Of course, we can start labeling too. I'd like to go back to that discussion of how we're going to do this. It seems there are a couple of extremes.

It's quite clear that industry has a lot of experience in these final formulation testing activities

based upon their activities with respect to proof of efficacy and safety. They have done some of these things, so we could learn a lot from them.

So, one extreme would be that, for example, we put out a call to industry between now and next meeting or the next meeting after that, a reasonable period of time, for suggestions for performance criteria from industry. Come into the committee maybe, say, a month before the meeting so we have a chance to read them and look at them, debate them at the meeting with industry, and then come up with some recommendation to the FDA either at that meeting or at a subsequent meeting.

The other alternative is, as I mentioned, is the task group. Now, this gets complicated because of the open nature of the deliberations. So, I'd like to put those two possibilities and any others that you might want to suggest as to how we might handle this issue of final formulation testing.

Lew?

MR. CANCRO: I think to get into a very open discussion about technical methods or whatever direction you're going to go in, really becomes almost a scientific symposium on the methods. So, my view would be that if you could look at this category, first of all, from single components -- let's start there -- and decide what you want

to confirm that this Category I ingredient is still active in a variety of products. The most expeditious way would be under whatever guidelines Andrea could tell us about to work in concert in looking over submissions by industry on the various ingredients, but to sort of condense it from a technical perspective. It could be an open meeting, and then a presentation of that for discussion among anybody who wants to make a comment on it.

DR. GENCO: Is your suggestion that we do that, that we go to the submissions for direction in terms of final product testing?

MR. CANCRO: Well, what I'm saying is that you can collect from industry their viewpoints on this, but to have that in a format where all you're discussing is methods and validation of the methods, it becomes a scientific symposium. So, what I'm suggesting is that they come into a smaller committee under whatever ground rules you're permitted to meet, which I'm sure Andrea could explain to us, and that they're looked at in terms of whether they meet your recognition for each of the classes of activity and then bring it to a forum where you can have discussion on how you've structured it, what you think is necessary. That's my suggestion. I hope I'm clear enough on it.

DR. GENCO: Andrea, do you want to make some

comments?

DR. NEAL: Let me just explain that this meeting is being conducted under the rules of the Federal Advisory Committee Act, more commonly known as the Sunshine Laws. For us to sort of get around that, you have to meet with less than three SGEs, special government employees, which you all are, at a time.

Now, I know that this has been done completely above board, et cetera with the committee that is looking at generic drugs. They often break into task groups I'm told and a couple of members of the committee will meet with representatives from industry or other outside sources, perhaps academia, wherever the expertise might lie, and then report back to the main committee.

Of course, there are some pluses and minuses to this. The pluses are you divide up the work. You I think maybe have a little bit more of an atmosphere that's conducive to that type of discussion. The down side is that sometimes the ins and outs of the discussion don't all get reported back to the main committee. So, I think those are the kinds of things that you need to think about as you decide what process you want to proceed with.

DR. GENCO: Dr. Soller?

DR. SOLLER: Bill Soller, NDMA.

We had some discussions during the break within

the industry group, and Lew, if I could just amplify on what you were saying. Just a couple of observations first and then a suggestion.

You've got, what, three Category I ingredients right now. You've got a host of Category III. The companies will want to upgrade III to Category I over time, and that will mean clinical data will be coming in to FDA because, as you mentioned, you have day jobs and there's a certain limitation to the time. I would expect that those clinical data would come in after this committee has disbanded.

Another observation. Under GMPs, what is done is that, for the most part, many of the detailed methods that we have in our plants aren't specified in the GMPs, but there are goals that are established for achieving strength, quality, purity, and identity and so on in the manufacturing process. Then it's up to the companies to validate that method, and then if it's inspected by FDA, you would have to show your methods are validated.

So, let me now put some of those concepts together.

The suggestion that we would have is that you deal just with the Category I ingredients now, that you ask the companies that have those Category I ingredients to submit information that they think would meet whatever you

define as your established objective or goal for the category. With anticaries, they wanted releasable fluoride and they had several other tests, some of which were shown there. But deal with it in a general way for that category as to what you think, get some thoughts on the table to help them as to what you think ought to be the performance objective, and let them come up with recommendations for tests that you could review.

I guess, Andrea, you had mentioned that two special government employees, SGEs, can meet without it being a public meeting, and if it's the kind of subgroup or task -- let me just go on for a second -- group like that that works perhaps with Lew, industry being on that, to sort through that information and come back without a decision being made, but the decision being made by the group, that would work. If it seemed better to be a public meeting to have that be done, that would work as well, but just give enough time for companies to get this together. That is for the category group, I group, that you have.

For the Category III group, I would suggest, once that process has gone through, you're now defining that you want to have some sort of performance standard built in for final formulation testing, and you would ask that those companies that are now going to submit information to the monograph process, to upgrade from

Category III to Category I, that at the time they submit those data for review by FDA, in order to get that Category III ingredient into Category I, they also submit what they think should be the performance criteria to ensure that final formulation testing that the panel wants.

That's basically the proposal we have.

DR. GENCO: Thank you. So that we understand this, you're suggesting that the panel set those performance issues or properties that we'd like some advice as to what tests might substantiate those.

DR. SOLLER: In order to give guidance to the companies, as they think about what they might submit to the panel. And maybe that is what you end up with, maybe it's not, but you'll determine that through the dialogue with the company.

DR. GENCO: Thank you.

Sure.

DR. NEAL: I'd like to just clarify one thing about the task group meetings that we've talked about. It's not that they're not an open meeting. They are an open meeting, but they're not announced in the Federal Register. There is not an official transcript taken of them if it's two or less SGEs. This little task group would actually take their own minutes. I could probably announce them on the information line and make people aware

of where they are and when they are, but they don't follow the full FACA guidelines or rules.

DR. GENCO: Thank you.

Lew?

MR. CANCRO: Bob, one additional comment. However, you're going to do this, either an open meeting or a committee assignment, you're looking at broad proposals which go from clinical testing for formulation changes of 6 months' duration to simply -- let me call it availability. I think to make the system work, this committee has got to, more or less, define where they want industry to help them. In other words, which of these two extremes are you looking at? I think that's the starting point so that you can get feedback. If it's going to be clinical testing or if it's going to be availability, that's the scope that has to be defined by you.

DR. GENCO: So, we have several suggestions on the table and maybe before we make some comments about the process and the scope -- Mrs. Buc, you would like to make a comment?

MS. BUC: Please, a brief one. I'm Nancy Buc from the law firm of Buc & Beardsley. I represent Pfizer.

I just want to note that final formulation testing, as you've heard from representatives of both FDA and some other speakers today, is very unusual and that

whatever may be the case for the Category I products that the panel intends to recommend, there are a number of the Category III products which aspire to Category I-ness, which may not need final formulation testing at all.

So, I'd like to suggest that the panel at least -- or ask that the panel at least keep in mind the possibility that the spectrum here is not from in vitro to 6-month clinical trials, that the spectrum is no final formulation testing on products that work, for example, by surfactancy and which, of course, must comply with other FDA requirements to make sure that what's supposed to be there is in there, but that no final formulation testing be very much among the possibilities that the panel keeps in mind because I think for many of the Category III ingredients, again whatever may be the case for Category I, final formulation testing may be wholly unnecessary.

Thank you.

DR. GENCO: Thank you.

Comments, questions? Yes.

MR. LONG: May I just make one brief comment? I'm David Long. I'm a lawyer with Warner-Lambert Company.

Warner-Lambert is obviously struggling internally with many of the same issues that the committee is struggling with now. We have not formally submitted a position yet. We would like to do that before the next

meeting in arriving -- I guess what we want to ensure and clarify is that no position, including a 6-month clinical trial, would be necessarily precluded from discussion before the next meeting.

DR. GENCO: I don't think that anything we've said says other than that. The whole spectrum. Maybe I misspoke in defining the spectrum, but clearly it's all the way from do you have the chemical entity in the product, which I understand all OTC has to show, to full clinical testing.

Yes.

DR. KATZ: In listening to the discussion, I agree that we need industry involvement to present to us the information about the different types of testing, and how best to approach this in the most expeditious way is often a problem.

In the past where we've needed a lot of input and where people have come in with a variety of different expertises and are in different places, we found it usually to be more expeditious to start off with sort of a task force working group as an open discussion of a panel rather than breaking up into the small subcommittee types of setup. It may be best again to ask industry to come forth at the next meeting, if that's when it's decided to be, or the meeting after that to present the information that they

have available and set it up again as a working type of a group where industry can present what they have available, that here people will gather, ask the questions that they have of industry representatives, and then sit as a total group to discuss the information, rather than break down into a task force.

DR. GENCO: Thank you. I think that it occurs to me that also three of us have reviewed the three products that are in Category I. So, maybe those individuals could be lead people in that discussion. So, the process could be a call to industry for suggestions by X date so that we have a chance to look at them before the next meeting, if that's reasonable, and then the three of us, Bill, myself, and Stan, be the lead discussants of each one of the three products. There seems to be some interest in dealing with them one at a time rather than as a pharmacologic class, and that be a major topic for the next meeting, if industry can prepare by that. Otherwise, we can do it two meetings hence, but the next meeting is really May. I think we've got the date.

So, there's a very concrete suggestion. I see a lot of heads shaking. Does anybody want to comment on that? Max, Gene?

DR. SAVITT: I would just hope that the data would be available for the entire committee prior to the

meeting.

DR. GENCO: Yes. That's the intent.

Dr. Soller suggested that we also do another thing and that is we come up with now some direction for what should be addressed.

So, let me go through the process again that's on the table, that we discuss today some of those issues that should be addressed. In other words, it would seem to me that we could discuss should antiplaque be part of it? Clearly antigingivitis should be part of it or its surrogate. Should antimicrobial be part of it as a surrogate? And these are the issues possibly, just to put them on the table.

Then if industry thinks that they can respond, let's say, one month prior to the next meeting with documents, we all get that information, or maybe six weeks, whatever, so that we have time to look at it, then Bill, myself, and Stan act as one-at-a-time lead discussants for, okay, here's what was submitted on stannous fluoride and Bill discusses that with his perspective, begins the discussion, we all discuss it, and then we go to the next one.

Then clearly I wouldn't guess that we'd be able to solve this at the next meeting. There would be yet another meeting with further input from industry and

anybody else and possibly two meetings hence which would be a year from now possibly that we might have some performance standards.

Now, that's not going to be the only thing we'll be doing. There will be other things.

How does that sound? It's open, plenty of opportunity for industry and anybody else to participate, lead discussants on the committee already have reviewed the materials. Max?

DR. LISTGARTEN: Sounds good.

DR. GENCO: Stan?

DR. SAXE: Yes.

DR. GENCO: Any comments from industry? Bill, this is kind of a version of what you've suggested.

DR. SOLLER: Sounds good.

DR. GENCO: And limited to Category I. Debbie? It's very complex. There are some Category III items in there that we have no idea of even the mechanisms, so it would be hard to address.

DR. KATZ: It's reasonable to begin this way.

DR. GENCO: Okay, thank you. Okay, good.

All right. Now, let's discuss some of the issues that we think should be -- oh, first of all, for the three Category I items, is there a feeling that there should be final formulation testing or is simply good

manufacturing practice and identification that the compound is there adequate? Is there a feeling that we need final formulation testing other than the existence of the compound in an unbound form in the product which is fairly standard?

DR. LISTGARTEN: I think we need final performance testing because they don't appear all by themselves. They're there in a complex formulation and we have to be sure that they do what they're meant to do.

DR. GENCO: Even though they're mouthrinses and not dentifrices. Dentifrices brings up a whole other level of complexity.

DR. LISTGARTEN: Are we only dealing with mouthrinses at this point?

DR. GENCO: That's a good question. There is a Listerine Cool Mint toothpaste. Have we put only Listerine mouthrinse in Category I or have we dealt with the toothpaste? Just the mouthrinse.

DR. SAXE: Well, I have a question. Does a toothpaste really contain those four essential oils?

DR. GENCO: Let's put it in a hypothetical situation. Can those Category I items be put into formulations other than mouthrinses and still be covered by the monograph, or can they be put into dentifrices?

MS. LUMPKINS: Once an ingredient is put into

Category I, the monograph doesn't limit in general. There have been certain specific instances where formulations have been limited to certain circumstances, but in general, once an ingredient goes in, it can be formulated as many different ways as the manufacturer can think up.

DR. LISTGARTEN: Listerine, for example, has a toothpaste as well as a mouthrinse. Now, most of us think of Listerine as a mouthrinse, but there is a Listerine toothpaste.

DR. SAXE: Mr. Chairman?

DR. GENCO: Yes.

DR. SAXE: I'd like the people from Warner-Lambert to respond, but I looked at a tube of that Listerine toothpaste and I couldn't find those four essential oils in the ingredients.

DR. GENCO: Is this an issue? The question is, is this an issue now? Are there products on the market, dentifrices and mouthrinses, with those Category I items or are they all mouthrinses?

MR. LONG: Dr. Genco, David Long from Warner-Lambert.

We have only submitted data on the mouthrinse. We are not submitting data on the current toothpaste product. It's not labeled for gingivitis. Yes, the Listerine ingredients are in the product, but they're not

active ingredients.

DR. GENCO: Dr. Bowen says that he reviewed stannous fluoride as both mouthrinse and toothpaste. Is that the company's understanding of what was approved or recommended for Category I? Was stannous fluoride in either formulation, mouthrinse or toothpaste?

DR. DOYLE: We would not limit that at this point.

DR. GENCO: So, we're already into a situation where we're dealing with toothpaste and mouthrinse formulations, so performance criteria should include, it would seem, ingredients that could be in either. There's a whole different set of ingredients in toothpastes that could inactivate as compared to mouthrinses. So, now it has reached a very high level of complexity. Am I correct in that?

MR. CANCRO: As you change dosage forms, it's quite likely that your concentrations of materials have got to change. So, in the scope of this review, that has got to be part of what you're deciding. At the present time, the Warner-Lambert people submitted information on a rinse with certain concentrations in a fixed ratio of ingredients. If the scope goes to another dosage form, I'm sure they would submit data to that extent.

DR. GENCO: Bill Soller suggested that we give

some guidance to industry. The guidance would be that since it's Category I, it can be put in any formulation legally, that at least those reasonable formulations be dealt with. In other words, performance criteria for toothpaste, performance criteria for mouthrinses. That's our intent then, okay.

Yes.

DR. WHITE: Donald White, P&G.

One consideration is that manufacturers will have to come up with a USP standard for the product form that they're in fact trying to test. If, of course, there's no clinical data available for a different product form, then they have to decide how they're going to define a USP standard.

In converting from a toothpaste to a mouthrinse or vice versa, someone mentioned that the concentrations may differ. That's correct because toothpastes are usually concentrated more because the toothpaste gets diluted during use. So, that's a factor that you'll have to consider because you're contemplating the concentrations that are going to be in the monograph. Of course, as you change forms, if those concentrations change, you need to deliberate what that will mean. Again, you have to take that back to a USP reference standard which can be used in testing.

DR. GENCO: Is that reasonably clear to the panel, and do we agree with that?

Does somebody want to articulate what the USP standard really means? It's a concentration in a formulation that was clinically shown to be effective? So, it's not only chemical but clinical activity.

Bill?

DR. BOWEN: Presumably if someone had the idea of incorporating an active agent into a dental floss, an appropriate USP standard would have to be developed also. Thank you.

DR. GENCO: Well, first of all, the panel feels that some performance criteria are needed beyond simple chemical identification of the active ingredient.

Secondly, the USP standard should be identified based upon the clinical studies.

Max, you brought up the point of antigingivitis versus antiplaque. You'd like to see both, or is antigingivitis sufficient?

DR. LISTGARTEN: I think we need to see both.

DR. GENCO: Let's discuss that.

DR. LISTGARTEN: Let me clarify, if I may. The original intent of developing active products was to control dental plaque in order to reduce gingivitis. Therefore, we need to really see both of these intents

fulfilled, namely, that the product will reduce dental plaque and control gingivitis.

My concern is that one could theoretically put in formulated cortisone toothpaste or some such thing which has no antimicrobial effect but simply acts on interfering with the inflammatory response that would not be the intent of what we want to accomplish here.

DR. GENCO: Presumably there's none of those in the Category I now. That's another discussion. In Category I, as I understand, we've been told that they're all antimicrobial.

So, is it necessary, in a final formulation testing, if it isn't the full clinical test, to have plaque reduction also, or is gingivitis reduction sufficient?

DR. LISTGARTEN: I think we have to demonstrate both.

DR. GENCO: Gene, do you want to comment?

DR. SAVITT: Yes, I would tend to agree with Max, but I'm hesitant to make decisions about what's needed until I get an idea of what kind of testing seems to be rational and be able to mull over the various tests.

DR. GENCO: I point out that in some of the studies, you will see a gingivitis effect and not a statistically significant plaque reduction. We have been very firm and clear in saying we require the gingivitis

reduction. The plaque reduction is a secondary characteristic or outcome that would support the activity, but isn't necessary to prove the activity. I think that has been our position.

So, now in a performance criteria, you're requiring maybe something even more stringent than we required for the original clinical data by requiring both plaque and gingivitis, it would seem to me.

DR. LISTGARTEN: Can you give me an example of what you had in mind?

DR. GENCO: Yes. I think that some of the Colgate data with triclosan. Some of the studies showed gingivitis inhibition and not statistically significant plaque inhibition. Fred, is that clear? I mean, that could theoretically happen and I think it has happened even with the stannous fluoride.

DR. OKARMA: Excuse me. If I could just interject for one second. The triclosan submission is a new drug application.

DR. GENCO: Right.

DR. OKARMA: It is not the purview of this review.

DR. GENCO: I know that, but I'm using that as an example. I'm trying to make a point.

DR. OKARMA: There was plaque reduction.

DR. SAVITT: It was stannous fluoride.

DR. GENCO: In our instance it was stannous fluoride.

DR. OKARMA: Yes. Plaque reduction was seen with the triclosan-containing product, and that is an approved label claim for Colgate toothpaste.

Thank you, Mr. Chairman.

DR. GENCO: Thank you.

Stan?

DR. SAXE: I was going to say I think this is an important point which we had worked over before, in that the endpoint is the gingivitis reduction. It may be we don't know the mechanism of why plaque -- the gross method we have now of assessing plaque is merely to look at the bulk of the plaque that's present on a tooth, and it may be that one agent will decrease the virulence of the plaque in a sense and make the plaque -- so the plaque in body, the mass may grow and be present, but it's not having an effect to cause the gingival inflammation.

So, again, our endpoint is gingival reduction, but if a product has been shown, as part of its mechanism perhaps, that there is plaque reduction as assessed by the methods now in use, then for that particular product it can be incorporated as part of the performance testing. So, it really is on a case-by-case basis for these Category I

products.

DR. GENCO: So, Gene, your suggestion was to wait to see what comes in.

DR. SAVITT: Yes. In mulling it over, since mechanisms are not a requirement for approval, we could have product that shifts the microbial flora to certain species that are less inflammatory to the tissues, but yet doesn't reduce the gross amount of plaque or the thickness or whatever type of test you might do. So, my feeling would be the emphasis should be on the gingivitis issue, although I can understand why the addition of plaque information could be of some use.

DR. GENCO: Bill?

DR. BOWEN: As far as I recall, all three submissions contained performance data. I thought that we are looking for methods that will circumvent the need for gingivitis in a plaque study, and these would include the performance data, for example, what is the bioavailability of the active ingredient in the mouth. Does the final formulation give the same performance data as the original test product over a shorter period of time? If we are going to require full clinical testing, as I think I'm hearing on the final formulation, well, there's no point in discussing it further.

DR. GENCO: No. I think the point is, is there

a surrogate for the 6-month clinical trial? Could there be a 2-week or a 1-month human or animal gingivitis and plaque? I just want to get the feeling so that this gives some direction to the companies as to what our view is of that.

Is there a feeling that that would be important? Some in vivo surrogate, not maybe the full clinical trial, although that's a possible outcome, something short of a full clinical trial, anywhere from a 4-day plaque inhibition to a 2-week experimental gingivitis to a 1- or 2-month dog experiment. There are smaller experiments that you could look at gingivitis, plaque or either alone, for example, 4-day plaque. This is really what I'm getting at.

What's our feeling, or do you want to wait to see what comes in for each product?

Or no in vivo? This is what you're suggesting. Maybe only in vitro is adequate.

DR. BOWEN: No. I like in vivo.

DR. LISTGARTEN: I think we may not need a 6-month trial, but we're going to need some in vivo evidence of antigingivitis effect. This could be either, as an example, a situation where the mouth is entirely cleaned, free of plaque, and we do a plaque growth inhibition study, or one could do an experimental gingivitis study, or one

could do a plaque reduction study where you have a lot of plaque to begin with and then you start your testing. These could be 2-3-week experiments rather than 6 months.

DR. GENCO: Bill?

DR. BOWEN: Sorry, Max. I misunderstood you. I see where you're coming from now. Thanks.

DR. GENCO: Any other comments? Christine?

DR. WU: I also tend to agree with Max, and I'd like to make a comment regarding what Max said earlier about minor formulation changes, especially in a mouthrinse, for example. What do we consider as minor? Sometimes just by changing the flavoring agent, one is using one essential oil versus another, and that could change the activity greatly.

Let's take Listerine for example. The combination mix has been approved. What if a company goes out and makes a mouthrinse that uses water as a vehicle instead of alcohol? That's not going to work, and do we need a performance test for that?

DR. GENCO: So, you're suggesting that any change in formulation from the formulation that was used for the clinical trials that we looked at, that there be performance criteria, any change, even though it's very minor.

DR. WU: I can't say exactly now but that's

what comes into my mind. For example, chlorhexidine. There are mouthrinses that are geared for children to use and there's chocolate flavors. There's all kinds of flavors and because of these changes in flavoring agents, there are some in vitro tests that have been done, and it's different.

DR. GENCO: So, what are you suggesting?

DR. WU: I'm suggesting that I can't make any decision right now, but I suggest that I'd like to think more about it and I'll think about what really -- I need to know what really constitutes minor changes.

DR. GENCO: So, we need some direction from industry as to what changes they have already found are inconsequential in terms of not affecting activity.

DR. WU: Yes, that would be nice.

DR. GENCO: For example, if you reduce the alcohol content from 26 percent to 19 or 22 percent, that may not be of consequence, but if you reduce it down to 10 percent, that may be of consequence. So, we need some direction from industry as to which changes are minor inconsequential and which changes might affect activity.

DR. WU: Right.

DR. GENCO: Okay, thank you.

Bill?

DR. SOLLER: Just a thought as you go through

this and thinking back as to what is happening with other categories. We had a discussion on vaginal spermicides late last year on this exact kind of issue, and we're in the process of setting up reference standards in that category. Of course, it has been done on fluoride.

I think what you're after is you're getting after this term "substantial equivalence." You're never going to have an identical product, but you're talking about having a substantial equivalence. I think it goes too far to start specifying inactive ingredients. I think what you're asking for is that whatever that particular test is, here are the active ingredients that can be used. It needs to be shown to be substantially equivalent to the reference standard, and if you come up with a water-based mouthwash or if you came up with an alcohol-based or who knows what based, but you show that you were the substantial equivalent in that performance, then that company would be achieving I think what you're after.

DR. GENCO: So, what you're saying is that every formulation has to be -- if we come up with the recommendation for final formula testing, it has to be subjected to the final formula testing no matter how small the change.

DR. SOLLER: No, no. I'm not necessarily saying that. I would like to reference Nancy Buc's comment

and say that I think you should be open to a manufacturer being able to demonstrate that it could be any one of whatever that spectrum is. So, at this point be open to that.

DR. GENCO: Right, including none.

DR. SOLLER: I was just trying to comment recognize you're dealing with actives when it comes to substantial equivalence and not the inactives. I don't think you have to do that because you're defining what you want that goal to be. You ought to take those actives and then formulate it in way that meets that goal against the standard that's being defined.

DR. GENCO: Is that clear?

(No response.)

DR. GENCO: Any other guidance for industry in terms of issues to be addressed in these performance standards or lack thereof?

I remind the panel again that we should be consistent in our view of plaque versus gingivitis. Already we've heard a recommendation for a performance standard which looks at plaque regrowth. Are we going to be comfortable with that if we've made such a point that gingivitis reduction was the key to approval? I just want you to think about it.

Max?

DR. LISTGARTEN: The suggestions I made before were nothing but suggestions. I didn't mean to imply that any one of these would be necessary or one could pick from a menu of things possibly and use one in vivo and one in vitro. I don't have anything in mind at the moment that I would want to suggest as the standard to follow. I would like to see what comes in from industry before I decide on what's suitable.

DR. GENCO: Is there anybody from industry that would like more direction? We're really striving to give direction here with incomplete information as to what's going to come in. But we just want to be helpful. I just don't want to leave here without being as helpful as we can because I know it's going to be a lot of effort for you to get these things together.

Yes?

DR. WHITE: Bob, I can't speak for the essential oil ingredients, but you already have our information submitted for the testing on CPC and stannous fluoride toothpaste, the CPC mouthrinse.

In addition, don't forget the USP standard for these products has been clinically proven for gingivitis. So, I'm a little uncomfortable. I don't see where we're going. We're vacillating in between needing to run an EG study -- if, for example, you decided that a short-term EG

study would be what you wanted, then A, you'd have to find a place where you can run an EG, which isn't necessarily trivial. B, you'd have to validate that that test can necessarily show that the USP standard is different than a placebo and so on and so forth.

So, you have to be careful where you're going. You could end up being years and years of work for an ingredient that's already been proven clinically effective and which can be easily studied by using a combination of, let's say, one in vitro test, a plaque regrowth test, and an animal test or something like that.

So, yes, we do need direction. You've already seen the set of tests that we've suggested for the ingredients which we have submitted. And moreover, you've seen our suggestion as to what the testing program could look like, and I'd ask you to look that over carefully.

DR. GENCO: Okay, fine.

DR. WHITE: And then maybe ask us from those submissions what it is that you'd like to see more of specifically.

DR. GENCO: I think one thing that's clear is that we're going to need some evidence that it's a true surrogate that is predictive, if you do X test.

Realize, all the things that we're discussing now are examples. We're not making any suggestions or

giving any feeling for what we might recommend. They're examples. So, rather than using vague examples, we use specific examples, but it doesn't mean that that's what we're thinking about. It's just an example.

So, I think one criteria is going to be that there is some evidence. And I can't imagine this committee not asking this question. You come up with your test X. It's a surrogate. What is the evidence that that is predictive of antigingivitis effect in the population over 6 months. That's really the kinds of things that we're probably going to ask questions about.

DR. LISTGARTEN: Or to put it another way, what you submitted is actually very useful information, but what I'd like to know is if I go into the business of producing a comparable product tomorrow and I don't want to repeat all the clinical trials you did, what do I need to submit in order to market my product if I want to produce something similar to yours but perhaps with a little change in formulation?

DR. WHITE: And additionally, in terms of validation of tests, we also had some suggestions about what it is you have to show. Now, if you go to the fluoride, it might be useful also to contemplate how the tests became arrived at. Or it's not good English, but you know what I mean. How they arrived at the tests for the

fluoride monograph for caries. For example, as we stated in our submission to you, it's reasonable that fluorine in a toothpaste should prevent cavities in an animal model. And it's reasonable that if you take the fluoride ingredient out of the toothpaste, the toothpaste should lose its activity. In fact, those models are validated in that way.

Is the amount of caries reduction in the animal exactly the same numerically, let's say, as the amount of caries reduction in humans at every time period that it's used? I'm not so sure anybody has ever proven that.

Similarly, it's reasonable that fluoride should be taken up in carious enamel in order for it to have an effect on the caries process. If you take the fluoride ingredient out of a toothpaste, or if you bind the fluoride up, do you see fluoride incorporated in the enamel? Yes or no? There's your correlation to the clinical endpoint.

So, my confusion is where you're going. If you're asking for the precise mechanism of action for all these ingredients, I'm not so sure I could ever get researchers to agree. If you're asking for the sort of validation criteria we're talking about, can you identify when the USP formulation is deactivated, can you see that it's deactivated, what is the dosage effects in the model, so on and so forth, those types of things can be done.

DR. GENCO: We're asking a very practical question. If you change the formulation, is it still active? And we saw examples of where it was inactivated inadvertently, so we're quite concerned about that. It's not mechanism.

Lew?

MR. CANCRO: Bob, reducing this to maybe some simple principles might get you to where you want to go. I think the first is that the drug must be there at an available concentration. That concentration has been determined by the data you've seen. You've seen data which says that this concentration -- it has done this. So, that's the first step: chemical interactions. If the manufacturer can't see chemical interactions, clearly it may be appropriate to stop there or to go on to a subsequent step.

But to try and look at this and say that the end test, whatever that's going to be, is predictive of chemical interactions is really the long way around. Start there and then, upon that premise, it is available. It's available at a concentration you've judged to be effective. What else do you need? And you've heard the spectrum that industry has presented. Some people say you should still go on and do clinical trials. Other people say that's enough, put it in your formula and stop there.

So, I can't give you guidance, but it always starts with the lack of chemical interaction or you don't go to the next step.

DR. GENCO: No. I think we want guidance for industry. This is a discussion for industry to give them a feeling for what we feel at this point, and I think we've done it.

Is there anything else you think we should discuss either from the panel or from industry or from the FDA? You have enough guidance. Go to it.

Is the time adequate between now and -- the meeting is what? May 8?

MR. SHERMAN: The next tentative meeting is May 27 and 28th, 1998.

DR. GENCO: May 27th, 1998. Is a month before that, April 27th, just so there's no confusion, to Andrea and then it will come to us or to Bob with multiple copies? I mean, let's make this efficient.

DR. COLLIER: I guess I'm not completely clear still on what you want. I guess the logistics. Do you want us to submit information? We've listened to the discussions and we know what your concerns are, but specifically are you asking for providing validation data? There are a lot of things we could provide. We've given principles and we've provided -- I guess I don't know

specifically what else we could provide for in fact CPC or stannous.

DR. GENCO: If you've already done it, then just maybe repackage it. If you think you've done it -- and maybe you have, but there are other companies. We don't have anything from other companies with respect to their products.

Or I suppose there could be a company who is thinking of making a me-too that would want to suggest what they would have to come up with.

DR. WHITE: Don White again from P&G.

In order to provide answers to your questions around the methods which we've detailed by May, perhaps if the committee could review in detail what we've submitted plus our planned tests and then come up with a set of specific questions, let's say, by February, then maybe we could address those by May. Specific sections of what we've submitted talked about performance testing. I'm not so sure what extra I could give you. If you want to review that and then ask some specific questions and give us four or five months to respond to those questions, I suppose that's something we could do.

DR. GENCO: So, the Procter & Gamble submission with respect to CPC and stannous fluoride. You're satisfied you've given us all the final formulation testing

suggestions that you would like to make. So, we'll look at those and we'll get to you then questions based upon those.

DR. WHITE: Right, including the submission that you received for this meeting, which is our recommendations for what the program might in general look like. You'll see from our submissions how they fit within the context of that program that we've suggested.

DR. GENCO: Okay, fine. Fair enough. We have a volunteer to prepare that.

Anything else then that we can be helpful with in terms of the industrial submission to us prior to next meeting?

(No response.)

DR. GENCO: Okay, fine.

Let's now go to the next topic and that is the foreign submission. Bob, do you want to give us some background on that?

MR. SHERMAN: Do you have the list in front of you?

DR. GENCO: Yes, I have the list here.

Could you just review again? I know you mentioned this at first, but just to refresh our memory.

As I recall, you would like this committee to evaluate the data submitted on this list of seven or eight compounds which companies have suggested that the FDA

approve as over-the-counter, put in the monograph based upon foreign data only.

MR. SHERMAN: Correct. It hasn't been determined at this time whether such data will be eligible for the OTC review. There is a proposal out that that be the case. In the past the agency has not included foreign data. There is a proposal where certain other conditions would be eligible for the OTC review, but while the panel is in session, we want to take advantage of the panel's expertise and get their view of whether these particular ingredients could be considered safe and effective. So, we in a sense want your opinion, but you will not actually classify them.

DR. GENCO: So, the opinion is whether there is a chance that these could be reviewed given the concerns that the FDA has already expressed, and we have that information relative to who the investigators are, the monitoring, the reporting of adverse effects, all those concerns about the foreign studies versus U.S. studies.

MR. SHERMAN: In other words, the review would be essentially the same, as if it were U.S. data, and then the reviews would be in the same form only those particular ingredients would not be classified. We will not formally put them in a classification. We won't make that recommendation, but other than that we will review the data

as if it did qualify for the review.

DR. GENCO: So, as part of the review, we're asked to look at the foreign-ness of it, that is the fact that it was done in another country and may not --

MR. SHERMAN: No, no. That's not your decision to make. You're just looking at the validity of the data itself. It later will be determined whether those ingredients will be eligible for the review.

DR. GENCO: The science as science, not whether it fulfilled the FDA requirements for good clinical practice, et cetera, whether it was monitored, those issues. Only scientific issues, not regulatory issues with respect to --

MR. SHERMAN: Yes, whether the evidence --

DR. GENCO: -- where it was done is at a GCP clinic --

MR. SHERMAN: -- support safety and effectiveness.

DR. GENCO: Just scientific.

MR. SHERMAN: Correct.

DR. GENCO: Is that clear? In other words, some of these may not be done in so-called GCP clinics. Some of these may not have been monitored the way the FDA would like them. Some of these may not have had adverse effects reporting, as the FDA would require for a U.S.

study, but we should not concern ourselves with that. Only the science. Is that a good study proving safety and efficacy.

MR. SHERMAN: Correct.

DR. LISTGARTEN: Well, there's good science and bad science done right here in the United States, and there's good science and bad science done abroad. Now, those that are good clinical trials run in foreign countries which I would certainly consider valid clinical trials, but it's on a case-by-case basis. I wouldn't automatically exclude a good clinical trial done in Europe, for example, or in certain European countries, from being a valid trial just because it's done in Europe and not in the U.S. By the same token, there are many things done here which are not too reliable. So, I'm not exactly sure what to tell you. If it's a good clinical trial, the fact that it's done abroad does not necessarily exclude its being considered.

MR. SHERMAN: I think the only issue that we're concerned with right now is whether there is evidence to support the safety and effectiveness of these ingredients as OTC products. That's all we're concerned with.

DR. GENCO: I bring this other issue up because in the handouts that we were given, these are the concerns of the FDA. In other words, there are requirements. You

have to keep the records for 15 years. There are things like that that maybe would not have been part of the study because it's not a U.S. study, but the science could be perfectly good, I agree. So, that's what we're being asked to judge, not how it fits in with the FDA's view of how this should have been done, but is it a good scientific project per se. Okay.

Now, we have a list of seven compounds.

MR. SHERMAN: Excuse me, Bob. Let me just say one thing that I may have forgotten to mention. In some cases there may be submissions for the same ingredient from more than one sponsor. So, in those cases even if an ingredient is withdrawn from the review, it would still be reviewed, but that review would be based only on the data that remains in the review. So, if a company withdraws an ingredient, it still may be reviewed.

MR. CANCRO: Bob?

DR. GENCO: Yes, Lew?

MR. CANCRO: And public information on the ingredient.

MR. SHERMAN: Yes.

DR. GENCO: Bob, with respect to these proposals, for example, the first one on my list is soluble pyrophosphate. This proposal comes from a company, so I understand this, and it's a submission of their data with

an antigingivitis effect. So, it's appropriate for us to look at this as if it were to be included in the monograph. You just want an opinion on this as an antigingivitis agent.

MR. SHERMAN: Yes, correct.

DR. GENCO: So, whoever agrees to do that review will get the submission from you and then we'll have at some point that review gone over by the committee with a recommendation for this is good science, not good science, or would you like the recommendation put into if everything else was the same, that this would be a Category I or Category III? I mean, to what extent? Just good science?

DR. KATZ: Good science.

DR. GENCO: Proof this is safe and effective. Period.

DR. KATZ: That's correct. We don't want you to categorize them.

DR. GENCO: Okay, good.

MR. SHERMAN: We won't categorize it, and I guess we'll give you more detail as to how we want it stated. But in a sense, we won't say I recommend such and such a category and take a vote on it.

DR. NEAL: I'm wondering if it might be helpful for the committee members to just give a very brief background on what the OTC proposal is for foreign

marketing data. Can you just provide a very brief thumbnail sketch of what the proposal is so that they can put this in some context?

MR. SHERMAN: The proposal is basically the definition of what material time and extent is and whether that includes marketing in a foreign country. Traditionally we've not accepted that as falling under that definition. Actually it was published as an advance notice of proposed rulemaking. So, the agency is actually asking for opinions on whether that is a reasonable proposal to make. So, it could be some time before that is actually decided. I know that certain sponsors are not comfortable with publicly discussing data that may not eventually qualify for the review, and that is why we've said that if that's the case, they may withdraw it at this time and they would be able to resubmit it later.

In other words, that decision has not been made yet, and some would say you're putting the cart before the horse in reviewing something that we don't even know would qualify. We're saying we don't want to have to call this panel together again. We have you here. We want to take advantage of your expertise to review the science.

DR. GENCO: All right. So, if everything went according to -- let's say it turned out that the foreign data was allowed by the FDA for OTC, then our reviews

given, let's say, in 1998 may be used in the year 2000 for your advice with respect to categorization.

MR. SHERMAN: Right. That could be --

DR. GENCO: So, our review should be at that extent in detail.

MR. SHERMAN: Yes, exactly.

DR. GENCO: Is that clear?

Bill Soller? Lew?

MR. CANCRO: When will it be appropriate for the public display of the ingredients that are being reviewed? Is that at the next meeting? It hasn't been provided here. We don't know what's being reviewed other than if you submitted it.

MR. SHERMAN: We'll tell you that right now because Dr. Genco will make assignments.

MR. CANCRO: Okay.

MR. SHERMAN: There have been some cases where some ingredients have already been withdrawn, but for now all we're going to do is list the ingredients, make assignments so nothing will be reviewed until the next meeting at the earliest.

MR. CANCRO: So, this list will constitute ingredients that have not been withdrawn by the sponsor.

MR. SHERMAN: Correct.

DR. GENCO: Is it clear now what we're being

asked to do? Bill?

Let me just go through the ingredients: soluble pyrophosphate, triclosan -- that's the second one. The third one is triclosan/zinc citrate. The fourth is chlorhexidine gluconate. The fifth is non-saponifiable fraction of corn oil. The sixth is hexetidine, h-e-x-e-t-i-d-i-n-e, and the last one is bromochlorophenol. It seems that there are seven.

MR. CANCRO: What was the last one?

DR. GENCO: Bromochlorophenol, b-r-o-m-o-c-h- --

DR. LISTGARTEN: Chlorophene.

DR. GENCO: Chlorophene? That's p-h-e-n-e.

Are there any volunteers? Bill Bowen will do the hexetidine.

DR. WU: I'll do the corn oil.

DR. GENCO: And Chris will do the non-saponifiable fraction of corn oil.

DR. LISTGARTEN: What are we actually supposed to do with these ingredients?

DR. GENCO: Let me see if I understand this. Just like you did before, except don't suggest a category. In other words, you'll go through the review. These studies have been done relative to safety, X, X, X.

DR. LISTGARTEN: For the other things we've

reviewed, we got piles of material. Are we going to get material to do --

MR. SHERMAN: You'll get the same piles.

(Laughter.)

DR. GENCO: Is it clear?

DR. LISTGARTEN: We're going to get something to help review on this.

MR. SHERMAN: Yes, you can count on it.

DR. GENCO: The reviews then, if I'm clear on this, may be two or three years hence if everything falls in place. We will be disbanded. The FDA will use these to put them into Category I, II, or III. So, they should be worded such that they can take that advice. This has been proven to be safe. It looks like that might be a Category I.

MR. SHERMAN: Is it the panel's opinion that there's enough evidence to support --

DR. GENCO: Yes. This has been proven to be effective against gingivitis. You're not saying it but it can be used by them to help classify.

DR. LISTGARTEN: Okay. I'll do pyrophosphate.

MR. SHERMAN: Exactly.

DR. GENCO: Excuse me?

DR. LISTGARTEN: I'll do pyrophosphate.

DR. GENCO: Gene?

DR. SAVITT: Well, I would suggest that there are people on the committee who are probably better qualified for chlorhexidine than I am. So, I'll take the last one. I'm a little hesitant to say triclosan because I can imagine the pile I'll get.

(Laughter.)

DR. SAVITT: But whatever you want to assign, let me know.

DR. GENCO: Stan? So, Gene is going to take bromochlorophene. And we have chlorhexidine and then the triclosan.

Are the triclosan and triclosan/citrate two separate submissions? Do you think we should have two separate people or can one person --

MR. SHERMAN: Are you talking about triclosan versus triclosan/zinc citrate?

DR. GENCO: Yes.

MR. SHERMAN: One is the single ingredient and one is the combination. It's two separate submissions.

DR. GENCO: Two separate safety and efficacy.

MR. SHERMAN: Right.

DR. GENCO: So, it looks like that should be two separate people.

So, Stan, we have left triclosan alone, the combination triclosan/zinc --

DR. SAXE: I'll do the triclosan/zinc citrate combo.

DR. GENCO: Okay.

MR. SHERMAN: I wanted to mention that I spoke to Sheila McGuire recently and she realizes that the person who's not here usually gets the assignment that no one else wants.

(Laughter.)

DR. GENCO: She understands that, yes.

MR. SHERMAN: So, she realizes that.

DR. GENCO: Sure. Sheila, you got triclosan.

(Laughter.)

DR. GENCO: That means I've got chlorhexidine. Is that it? Is that everybody?

Is that clear? Let me go over those again. Soluble pyrophosphate, Max Listgarten. Triclosan, Sheila McGuire, or Sheila McGuire, dash, whatever, when she comes back. She's getting married I understand. Triclosan/zinc citrate, Stan. Chlorhexidine I will do. Corn oil, Chris. Hexetidine, Bill Bowen. And bromochlorophene, Gene Savitt.

What's the timetable now on this?

MR. SHERMAN: Well, we need to go through the submissions and see how much is involved and we'll get to that later. I'm not sure exactly what will be done at the next meeting.

DR. GENCO: So, the assignments to present could be made at next May's meeting.

MR. SHERMAN: Could be but not necessarily depending on the amount of material involved and the availability of the subcommittee to do those reviews.

DR. GENCO: Great.

So, it looks like at the next meeting we'll focus on the final formulation testing. We'll have had this information from industry a month before. We'll have looked at it before then. Bill Bowen is going to get to us and then to P&G questions about the P&G submission.

DR. BOWEN: Stannous fluoride.

DR. GENCO: Stannous fluoride alone? Okay.

How about the CPC? I could take a look at that. I reviewed it.

So, I will get the CPC. Bill will get the stannous fluoride questions.

Then at the committee meeting we will discuss these submissions from companies interested in the fixed combination, the Listerine product, and stannous fluoride and CPC. Those would be the three. Performance standards for each one of those will be discussed separately.

MR. CANCRO: Is Stan getting the fixed combination of flavoring oils?

DR. GENCO: There's no submission from Warner-

Lambert, I don't think, with respect to the performance criteria. Mike, do you want to address that?

DR. BARNETT: No. There will be a submission.

DR. GENCO: So, by end of April, Warner-Lambert will submit, or whatever. There will be a submission on that, the Listerine fixed combination.

We already have the submissions on the other two. We're going to review them.

At that point we would ask Stan to be the point person for discussion of the Listerine submission, and then Bill and I will be the point people for the other two.

MR. CANCRO: And you're not entertaining at this time going beyond the three that you've classified. Is that correct?

DR. GENCO: Yes, unless the panel, committee, wants to do differently, but I think we have our hands full with those three at least for the next meeting or two. I think we should reconsider, maybe everybody take a look at the Category III to see what's in there. Is it doable? Is Bill Soller's suggestion the reasonable one? Maybe, maybe not. Maybe something will fall out. I haven't looked at that list in a while, so maybe something will fall out that will be useful with Category III. And Debbie suggested we do that, so I don't want to leave that out of hand. But the priority, the focus could be on Category I for the next

meeting or two. Reasonable?

MS. LUMPKINS: Yes.

DR. GENCO: Debbie, could I ask you to give us the labeling? We're going to work labeling and final formulation together. We're going to focus on final formulation, but we're not going to forget about labeling. We'll talk about labeling at each meeting, and finally that will be our major focus. Could you give us a review of what the fluoride in children labeling is presently on toothpastes?

MS. LUMPKINS: On this one, we get to split the difference. For toothpastes and gels and those kinds of formulations, the lower age limit is 2 years of age. For powdered dosage forms, the lower age limit is 6 years of age, and for the more concentrated fluoride preparations, the lower age limit is 6 years of age. So, there's kind of a mix depending upon what you're talking about.

DR. GENCO: Thank you.

Any further items you think we should discuss now? We've got the date set for the next meeting. We've got pretty much the agenda, or at least the focus of the agenda for the next meeting. Bob?

MR. SHERMAN: I just want to mention that we want to try to finish up on Xylitol that was reviewed by Dr. McGuire and the combination of hydrogen peroxide, zinc

chloride, sodium citrate, and sodium lauryl sulfate that was reviewed by Dr. Listgarten. Apparently there will be a presentation on that at the next meeting. We'd like to finish up with the voting on that.

Then I can announce the future tentative dates. The next one would be, as I said, May 27th and May 28th, 1998. That's a Wednesday and Thursday. Actually they're all Wednesdays and Thursdays. May 27 to 28, 1998; October 7th and 8th, 1998; December 2nd and 3rd, 1998. I have my doubts about that one. That's less than two months from the previous one, so I'm not sure about that one. But we should be good for at least the next two.

DR. GENCO: Thank you.

Any further comments?

(No response.)

DR. GENCO: Well, I'd like to thank Bob. He has done a tremendous amount of work to get this meeting together with the prepared summary. You went through a lot of information, as did Andrea, and made my task very simple with that summary. I hope that was useful and I thank you both.

I'd like also to thank Bill and Stan and Gene for their review of the four products that we voted on, and I'd like to thank all of those in attendance here for being very cooperative. I see a very interactive, cooperative

atmosphere here between you folks and us folks, and I think we're getting a lot done. I am very pleased and proud to be working with you all.

Before we go, I'd like to also wish Andrea happy birthday.

(Applause.)

DR. GENCO: Take care. See you in May.

(Whereupon, at 11:46 a.m., the subcommittee was adjourned.)